Scand J Med Sci Sports 2012: 22: e79–e85
doi: 10.1111/j.1600-0838.2012.01499.x

SCANDINAVIAN JOURNAL OF
MEDICINE & SCIENCE
IN SPORTS

Short-term intermittent hypoxia reduces the severity of acute mountain sickness

M. Wille[1], H. Gatterer[1], K. Mairer[1], M. Philippe[1], H. Schwarzenbacher[2], M. Faulhaber[1], M. Burtscher[1]

[1]Department of Sport Science, Medical Section, University of Innsbruck, Innsbruck, Austria, [2]Dienstleistungen GmbH, ZuchtData EDV, Wien, Austria
Corresponding author: Maria Wille, MSc, Department of Sport Science, Medical Section, University of Innsbruck, Fürstenweg 185, 6020 Innsbruck, Austria. Tel: +43 512 507 4443, Fax: +43 512 507 2656, E-mail: maria.wille@uibk.ac.at

Accepted for publication 14 June 2012

Intermittent hypoxia (IH) is a promising approach to induce acclimatization and hence lower the risk of developing acute mountain sickness (AMS). We hypothesized that a short-term IH protocol in normobaric hypoxia (7 × 1 h to 4500 m) effectively increases the hypoxic ventilatory response (HVR) and reduces the incidence and severity of AMS. Therefore, 26 men (25.5 ± 4.4 years), assigned in a double-blinded fashion to the hypoxia group (HG) or placebo group (PG), spent 8 h at 5300 m before (PRE) and 2 days after cessation of the IH protocol (POST). Measurements included the evaluation of the Lake Louise Score (LLS) and the HVR. The severity of AMS decreased from PRE to POST in the HG (from 6.0 ± 2.7 at PRE to 4.1 ± 2.1 at POST), whereas the LLS in the PG stayed high (from 5.7 ± 2.9 to 5.5 ± 2.8, respectively). The HVR in the HG increased from 0.73 ± 0.4 L/min/% at PRE to 1.10 ± 0.5 L/min/% at POST and did not increase in the PG. The reduction of the LLS was inversely related to the changes in the HVR (r = –0.434), but the AMS incidence was not different between the HG and the PG at POST. In conclusion, short-term IH reduced the severity of AMS development during a subsequent 8-h exposure to normobaric hypoxia.

The World Health Organization estimates that worldwide, approximately 35 million visitors travel to altitude destinations above 3000 m annually (Martin & Windsor, 2008). The development of high altitude illness is linked to rapid ascents of non-acclimatized mountaineers above 2500 m, and acute mountain sickness (AMS) represents the most common high altitude syndrome. The associated symptoms are headache, dizziness, nausea, vomiting, loss of appetite, fatigue, and insomnia, which typically occur within 6–12 h after ascent (Hackett & Roach, 2001).

AMS is directly related to the absolute altitude reached (Hackett et al., 1976; Maggiorini et al., 1990; Schneider et al., 2002; Mairer et al., 2009, 2010), the rate of ascent, and is inversely related to the degree of acclimatization. Those who ascend faster and acclimatize less days on the way to high altitude show a higher AMS incidence than those who gradually climb higher (Hackett et al., 1976; Kayser, 1991; Murdoch, 1995; Schneider et al., 2002).

A promising approach to induce acclimatization and thus reduce the risk of developing AMS is the use of intermittent hypoxia (IH) by simulated altitude exposures, whether administered in hypobaric or normobaric altitude (Burtscher et al., 2008). IH possesses the advantage of exposing individuals to short-term and high degrees of hypoxia, but can avoid some of the detrimental effects associated with prolonged hypoxemia such as pulmonary and cerebral edema or symptoms of AMS (Bärtsch et al., 2004). Applied in hypobaric hypoxic chambers, i.e., similar conditions to real altitude, or in normobaric hypoxic chambers, IH also provides an alternative to a few days of continuous altitude residence for acclimatization (saving of costs and time).

Only a limited number of studies evaluated whether IH at simulated altitude – the majority using hypobaric hypoxia – has the potential to prevent AMS. Most of these studies used long-term IH protocols (≥3 h) over several days to weeks, at an altitude ranging from 2500 to 4300 m. These results show that AMS can effectively (Beidleman et al., 2004; Kolb et al., 2004; Muza et al., 2006; Dehnert et al., 2009) or partially (Schommer et al., 2010, Fulco et al., 2011) be reduced by IH. The demonstrated AMS reduction was associated with induction of ventilatory acclimatization (Beidleman et al., 2004; Burtscher et al., 2008; Muza et al., 2010).

Various IH protocols, lasting from minutes to several hours and differing degrees of hypoxia [inspired oxygen fraction (F_IO_2) of 10–15.5%], have been shown to induce ventilatory acclimatization (Sheel & MacNutt, 2008), both in normobaric hypoxia (Garcia et al., 2000; Bernardi et al., 2001; Foster et al., 2005; Katayama et al., 2005, 2007, 2009; Lusina et al., 2006) and in hypobaric

hypoxia (Benoit et al., 1992; Casas et al., 2000; Katayama et al., 2001). Arterial oxygen saturation (SpO_2) may improve under hypoxic conditions (Katayama et al., 2001), thus counteracting the increased hypoxemia that has been associated with AMS (Bärtsch et al., 2002; Burtscher et al., 2004; Loeppky et al., 2008; Mairer et al., 2009; Karinen et al., 2010).

So far, only long duration IH protocols with daily IH exposures of ≥3 h for 1 week or repeated exposures (>1 h) for several weeks have been tested for the effectiveness to prevent AMS. When considering that short-term IH protocols may be as effective in inducing ventilatory acclimatization as longer ones (Katayama et al., 2009), we hypothesized that a short-term IH acclimatization protocol, i.e., 1 h/day for 7 days at F_iO_2 12.6%, can prevent AMS symptoms during a subsequent exposure to normobaric hypoxia.

Methods

Subjects

Thirty healthy men (age: 25.9 ± 4.9 years; body mass: 78.6 ± 8.4 kg; height: 182 ± 10 cm) were recruited to participate in the study and gave written informed consent. As four subjects missed the retest, the following analysis was performed with the remaining 26 men who completed all tests. Exclusion criteria were reported to be cardiovascular, respiratory, and neurological diseases, migraine, chronic headache, permanent residence >1000 m, an overnight stay at altitudes >2500 m in the previous month, and exposure above >2500 m 2 weeks prior to the starting of the tests, as well as during the whole investigation period. The study took place in the laboratory of the Department of Sport Science, University of Innsbruck, at 600 m a.s.l. Subjects were not informed about the placebo-controlled, double-blinded study design. We considered this to be ethically acceptable as we did not promise improvement of performance and the study outcome had no direct relevance to the subjects. The study had been approved by the ethics committee of the Medical University of Innsbruck.

Study design

The subjects were exposed 8 h to normobaric hypoxia (PRE) at an inspired oxygen fraction (F_iO_2) of 11.3% (5300 m). Thereafter, the subjects were randomly assigned in a double-blinded, stratified fashion to the hypoxia group (HG) or the placebo group (PG) (characteristics of groups in Table 1). For stratification, the subjects were ranked according to their highest Lake Louise Score (LLS) at PRE and then assigned alternately to the HG and PG. The two groups did not differ regarding AMS incidence at PRE, highest LLS, hypoxic ventilatory response (HVR), and SpO_2 values at PRE, history of AMS symptoms, age, body mass index (BMI), altitude of permanent residence, or highest altitude reached (Table 1). The allocation of the subjects into the respective groups and the measurements during the IH sessions were performed by co-workers who were not involved in any analysis or other tests during the study. The IH acclimatization protocol started not less than 4 weeks after the first 8-h exposure. None of the subjects ascended above 1600 m 4 weeks prior to, or during, the IH exposures. Two days after cessation of the IH protocol (POST), the subjects spent again 8 h at F_iO_2 11.3%.

IH acclimatization protocol

The IH protocol consisted of episodes of 1 h/day at F_iO_2 12.6% or placebo (F_iO_2 20.9%, 600 m) for 7 consecutive days. The IH sessions were performed in two normobaric hypoxic chambers (hypoxic room systems; Hypoxico OHG, Traunstein, Germany) as the HG and PG were exposed during the same days. The number of subjects exposed at one time did not exceed five people during the IH sessions or the 8-h exposures. During the IH sessions, SpO_2 was measured and the LLS was assessed before and after 25 and 55 min of exposure. Values were not visible for the subjects. All subjects thought that they received hypoxia in the IH sessions as they did not know that it was a placebo-controlled study design.

Table 1. Baseline characteristics of the hypoxia group (HG) and the placebo group (PG) prior to starting the intermittent hypoxia (IH) acclimatization protocol

	HG	PG	*P*-value
n	13	13	
Age (years)	24.9 ± 4.5	26.0 ± 4.4	0.5
BMI (kg/m^2)	23.8 ± 2.3	23.1 ± 1.3	0.4
Altitude of permanent residence (m)	608 ± 73	627 ± 110	0.6
Highest altitude reached (m)	3,466 ± 860	3,537 ± 658	0.8
History of AMS symptoms (*n*)	2	3	0.5
PRE-test values			
AMS incidence_PRE (%)	92.3	76.9	0.3
Highest LLS_PRE	6.0 ± 2.7	5.7 ± 2.9	0.8
SpO_2 in hypoxia_PRE (%)	74.7 ± 5.2	73.2 ± 3.6	0.4
HVR_PRE (L/min/%)	0.73 ± 0.4	0.81 ± 0.5	0.6

Values are presented as means ± SD, numbers, or frequencies (%). *P*-value calculated with unpaired *t*-test or Fisher's exact test as appropriate.

BMI, body mass index; AMS, acute mountain sickness; PRE, 8-h hypoxic exposure to F_iO_2 11.3% 4 weeks before the IH acclimatization protocol started; LLS, Lake Louise Score; SpO_2, arterial oxygen saturation; HVR, hypoxic ventilatory response.

Eight-hour hypoxic exposure before (PRE) and 2 days after the IH acclimatization (POST)

At PRE and POST, the same course of action was followed. The subjects visited the laboratory in the morning hours and a short clinical routine examination was performed. The subjects abstained from caffeine and alcohol intake for at least 12 h and from strenuous exercise for 24 h prior to the measurements. Before entering the normobaric hypoxic chamber, baseline measurements including evaluation of the LLS, determination of the HVR, SpO_2 values, heart rate (HR), and hemoglobin (Hb) and hematocrit (Hct) measurements were performed. During the 8-h hypoxic exposure, resting measurements after 30 min and after 2, 4, 6, and 8 h included assessment of the LLS, SpO_2, and HR. Hb and Hct measurements were repeated at the end of the hypoxic exposure. During the trial, the subjects rested in a sitting position, watching DVDs, reading, or listening to music. They were allowed free control of fluid and caloric intake. F_iO_2 and inspired fraction of carbon dioxide (F_iCO_2) in the hypoxic chamber were kept at 11.3 ± 0.2% and 0.5 ± 0.1%, respectively.

Measurements

Assessment of AMS

Incidence and severity of AMS was assessed using the self-reported questionnaire of the LLS (Roach et al., 1993). Of the five symptoms listed (headache; gastrointestinal symptoms such as

anorexia, nausea, or vomiting; fatigue and/or weakness; dizziness and/or light headedness; and sleep disturbances), the subjects rated regarding of their status: 0 for no discomfort, 1 for mild symptoms, 2 for moderate, and 3 for severe symptoms. As the subjects did not stay overnight in the hypoxic chamber, the symptom complex 'sleep disturbances' was excluded. The subjects were classified as having AMS when the symptom headache was present and at least one other symptom, with a total score of ≥4 (Bärtsch et al., 2004). This score had to be attained after either 6 or 8 h. Besides, two subjects who vomited spontaneously during the 8-h exposure (one after 6 h and the other one after 8 h) in hypoxia, both in the HG, were rated as having AMS as they seemed seriously affected by the altitude, although headache was not present (West, 2011).

HVR

HVR was determined using a progressive isocapnic hypoxic test (Weil et al., 1970). After resting in a sitting position for 20 min, the subjects were connected to a re-breathing circuit. Expired minute ventilation (V_E) was determined breath by breath, and end tidal partial pressure of CO_2 (PET_{CO_2}) (Oxycon Mobile, Jäger, Germany) and SpO_2 (Pulsox-3i; Minolta, Osaka, Japan) were recorded continuously. PET_{CO_2} was held stable (±mmHg) by drawing part of the expired air through a CO_2 absorber. The test was terminated when SpO_2 dropped to 75%, which took an average of 5 min to do so. HVR was estimated as the slope of the line calculated by linear regression relating changes in V_E to SpO_2 ($\Delta V_E/\Delta SpO_2$, L/min/%), with slopes presented as positive numbers by convention (Katayama et al., 2009). HVR was assessed before entering the hypoxic chamber at PRE and POST.

SpO_2 *and HR*

Mean values of 5-min recordings of SpO_2 values were obtained by finger pulse oximetry (Pulsox-3i, Minolta) while subjects were resting in a sitting position before entering the chamber and after 30 min, 2, 4, 6, and 8 h in hypoxia, or after 25 and 55 min during the IH sessions. HR was monitored with Polar S810, RS800CX (Polar Electro OY, Kempele, Finland).

Hb and Hct

For the determination of Hb and Hct, blood samples (20 µL) were taken from the participant's fingertip and were analyzed (Miniphotometer plus LP 20; Hach Lange, Berlin, Germany) in normoxia and at the end of each 8-h hypoxic exposure.

Statistical analysis

According to the data from Burtscher et al. (2008), who found a reduction of 66.6% in AMS incidence through a short-term acclimatization protocol (1–2 h/day for 5 days at F_iO_2 15.5–11.0%) and an expected AMS incidence of 50% at 4500 m (Maggiorini et al., 1990; Bailey et al., 2006), the calculated power amounts to 90% ($\alpha = 0.05$) for the chosen sample size. Main outcomes of our study were the LLS, AMS incidence, and HVR. The Kolmogorov–Smirnov test was used to assess normal distribution of variables. A two-way analysis of variance (ANOVA) (group × time) for repeated measurements was performed to assess changes over time (normoxia to repeated measures in hypoxia, PRE to POST), with group (HG vs PG or AMS+ vs AMS–) as an independent factor. During PRE, two subjects abandoned the altitude chamber after 4 h and two after 6 h due to severe symptoms. At POST, two subjects left after 4 h and one after 6 h. Missing values of the LLS after 4 and 6 h were replaced with the last recorded LLS of these subjects, respectively, and included into the analysis (ANOVA for repeated measurements) to avoid a potential bias. Post-hoc Student's *t*-tests with Bonferroni correction were used. Unpaired *t*-tests were used to evaluate differences between groups (AMS+ vs AMS– or HG vs PG). Pearson's correlation analyses were applied to assess the relationship between the differences (POST minus PRE) of HVR (ΔHVR) and LLS (ΔLLS) as well SpO_2 after 30 min, with the highest obtained LLS. Qualitative and not normally distributed data were assessed with non-parametric statistics (McNemar, Fisher's exact test, and Wilcoxon). The statistical analysis was assessed for 26 subjects as four subjects missed the retest. HVR measurements of four subjects, two from the PG and two from the HG, had to be excluded due to technical problems. Data are presented as means ± standard deviation (SD), standard error of the mean (SEM) in figures, or frequencies as appropriate. A *P*-value of <0.05 (two-tailed) was considered to indicate statistical significance. Data analyses were conducted with the use of the statistical software package PASW Statistics 18 (SPSS Inc., Chicago, Illinois, USA).

Results

IH acclimatization protocol

Changes in SpO_2 values throughout the IH acclimatization protocol (7 × 1 h at F_iO_2 12.6% or placebo) were not significant (ANOVA for repeated measurements). In the HG, SpO_2 was 78.9 ± 4.8% in the first IH session and 80.5 ± 3.5% in the last IH session. SpO_2 in the PG amounted to 96.5 ± 0.5% at the first day and 96.7 ± 0.9% at the last day of IH, respectively. F_iO_2 during the IH sessions was kept at 12.6 ± 0.1% for the HG or at F_iO_2 20.9 ± 0.2% for the PG.

Eight-hour hypoxic exposure (PRE, POST)

Severity of AMS

The LLS increased over time at altitude, which was a consistent finding at PRE and POST ($P < 0.001$, Fig. 1). The changes in the LLS from PRE to POST were significantly different between the HG and PG ($P < 0.05$, two-way ANOVA for repeated measurements, group × time). While the LLS was reduced in the HG at POST ($P < 0.01$), the changes in LLS in the PG from PRE to POST were not significant (Fig. 1). The individually highest obtained LLS during the 8-h exposure at PRE and POST was reached after 8 h, except for five subjects who reached their maximal LLS before (after 2 h, $n = 1$, after 4 h, $n = 3$, after 6 h, $n = 1$). At PRE, the highest obtained LLS decreased from 6.0 ± 2.7 to 4.1 ± 2.1 at POST in the HG, compared with 5.7 ± 2.9 and 5.5 ± 2.8 in the PG, respectively (see Fig. 2). The AMS symptoms gastrointestinal upset and dizziness were significantly reduced from PRE to POST in the HG only ($P < 0.01$). No changes were detected regarding the AMS symptoms headache and fatigue/weakness.

Incidence of AMS

During PRE, 85% ($n = 22/26$) developed AMS. The changes in the AMS incidence from PRE to POST for the HG and PG are shown in Table 2. After the IH accli-

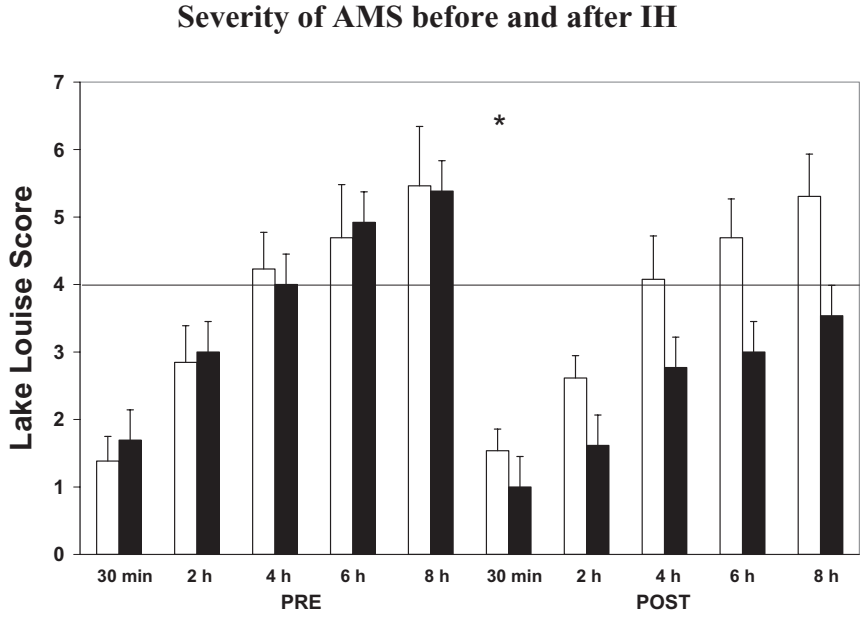

Fig. 1. Mean Lake Louise Score (LLS) with standard error of the mean after 30 min and 2, 4, 6, and 8 h in normobaric hypoxia (F_iO_2 11.3%, 5300 m) at PRE and POST [before the intermittent hypoxia (IH) acclimatization and 2 days after IH cessation, respectively]. The white bars represent the placebo group and the black bars the hypoxia group. The continuous line indicates the cut-off score for acute mountain sickness (AMS) diagnosis. *Changes from PRE to POST were significantly different between the two groups ($P < 0.05$).

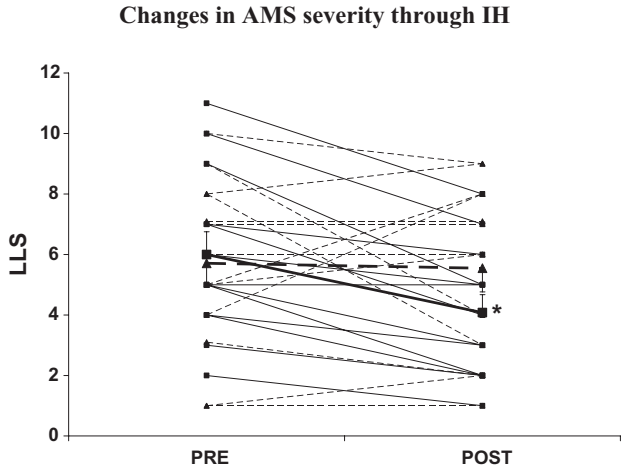

Fig. 2. Highest obtained Lake Louise Score (LLS) before (PRE) and 2 days after the intermittent hypoxia (IH) acclimatization (POST). The continuous lines with squares represent the hypoxia group (HG, n = 13) and the dotted lines with triangles the placebo group (PG, n = 13). Mean LLS ± standard error of the mean for the two groups are represented in thicker lines. *Significant difference from PRE to POST for the HG ($P < 0.05$). ΔLLS from PRE to POST was significantly different between the HG and PG.

matization, the AMS incidence in the HG was reduced by 39%, showing a tendency in reduction ($P = 0.06$), whereas the AMS incidence in the PG was reduced by only 8% (see Table 2). Differences in AMS incidence between the HG and PG were non-significant at PRE and at POST.

Table 2. Acute mountain sickness incidence for the hypoxia group (HG) and placebo group (PG) during the 8-h hypoxic exposure at F_iO_2 11.3% (5300 m) before (PRE) and 2 days after the intermittent hypoxia acclimatization (POST)

	HG $n = 13$ (%)	PG $n = 13$ (%)	*P*-value
PRE	12 (92.3)	10 (76.9)	0.3
POST	7[t] (53.8)	9 (69.2)	0.3

Values are presented as frequencies (%). *P*-value for differences between groups calculated with Fisher's exact test.
[t]Different by trend ($P = 0.06$) compared with PRE within HG (McNemar).

HVR

Changes in the HVR from PRE to POST were significantly different between the HG and PG ($P < 0.01$, ANOVA, group x time interaction) and are shown in Fig. 3. While HVR increased significantly in the HG, from 0.73 ± 0.4 L/min/% at PRE to 1.10 ± 0.5 L/min/% at POST ($P < 0.01$), the changes in the PG were not significant (0.81 ± 0.5 to 0.66 ± 0.4 L/min/%, respectively). ΔHVR was related inversely to ΔLLS ($r = –0.434$, $P < 0.05$).

SpO_2

SpO_2 of both groups decreased significantly from 96.8 ± 0.9% in normoxia to 73.9 ± 4.5% after 8 h in hypoxia (F_iO_2 11.3%) at PRE ($P < 0.001$) and reached 71.8 ± 4.8% at POST, a non-significant change. No dif-

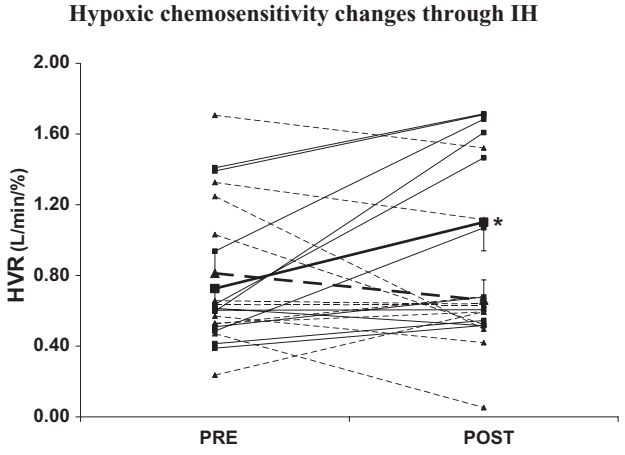

Fig. 3. Hypoxic ventilatory response (HVR) before (PRE) and 2 days after the intermittent hypoxia (IH) acclimatization (POST). The continuous lines with squares represent the hypoxia group (HG, n = 11) and the dotted lines with triangles the placebo group (PG, n = 11). Mean HVR ± standard error of the mean for the two groups are represented in thicker lines. *Significant difference from PRE to POST for the HG ($P < 0.05$). ΔHVR from PRE to POST was significantly different between the HG and PG.

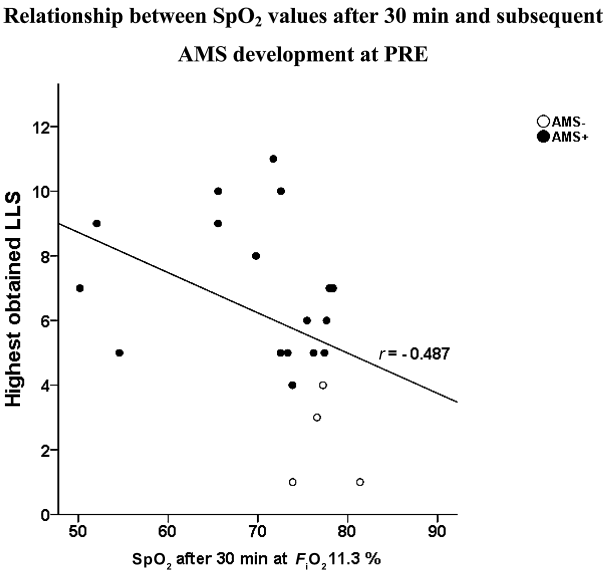

Fig. 4. Relationship between arterial oxygen saturation (SpO_2) values after 30 min and the highest obtained Lake Louise Score (LLS) during the 8-h hypoxic exposure to F_iO_2 11.3% at PRE. The filled circles represent those who developed acute mountain sickness (AMS) (AMS+, n = 17) and the open circles those who stayed well (AMS–, n = 4). At POST, no correlation was found between these two variables.

ferences in SpO_2 were found between the HG and PG at any time point measured. At PRE, mean SpO_2 values were significantly lower in AMS+ compared with AMS– (73.0 ± 3.3% vs 77.3 ± 4.3%, respectively, $P < 0.05$) and correlated negatively with the mean LLS at PRE ($r = –0.537$, $P < 0.01$). Also, SpO_2 values after 30 min correlated negatively with the highest obtained LLS at PRE ($r = –0.487$, $P < 0.05$; Fig. 4) but this was not found at POST, where the differences between AMS+ and AMS– were not significant (72.1 ± 5.6% compared with 71.7 ± 4.2%). Changes in SpO_2 from PRE to POST were not related to the changes in the LLS.

HR

HR of both groups increased significantly from 65 ± 9 beats/min in normoxia to 83 ± 12 beats/min after 8 h at PRE and to 83 ± 10 beats/min at POST ($P < 0.001$). The changes in HR from PRE to POST were not significant and no differences could be detected at any time point between the HG vs PG and AMS+ vs AMS–.

Hb and Hct

Changes in Hb and Hct were not significant from normoxia (15.7 ± 0.9 g/dL and 47.1% ± 3.2%, respectively) compared to the end of the 8-h hypoxic exposure at PRE (15.6 ± 1.3 g/dL and 46.2% ± 2.9%) or at POST. Values were not different between the HG vs PG and AMS+ vs AMS– at any time point measured.

Discussion

The major findings of this study are that short-term IH reduces the LLS, a measure of AMS severity. The reduction of the LLS is associated with an increase in hypoxic chemosensitivity, although the relationship is minor.

To our knowledge, this is the first well-controlled study to report that a short-term (1 h/day for 7 consecutive days) IH acclimatization protocol can effectively reduce AMS severity 2 days after IH cessation. In an observational study by Burtscher et al. (2008), where subjects were exposed 1–2 h for 5 days in normobaric hypoxia (F_iO_2 15.5–11.0%) before going to altitude, the AMS incidence was reduced by 66.6%. In the present study, the AMS incidence was reduced by 39% in the HG ($P = 0.06$) and by 8% in the PG (non-significant change).

So far, studies on prevention of AMS through IH are scarce and only long-term protocols were reported, i.e., IH exposures of ≥3 h for days (Kolb et al., 2004; Muza et al., 2006; Fulco et al., 2011), weeks (Beidleman et al., 2004; Dehnert et al., 2009), or repeated IH sessions >1 h over 4 weeks (Schommer et al., 2010). The majority of these proved to induce acclimatization effectively and thus reduce the AMS incidence. Beidleman et al. (2004) demonstrated a significant prophylaxis against AMS, exposing a small group of six subjects to 3 weeks of IH (4 h/day, 5 days/week to 4300 m), reducing the incidence of AMS from 50 ± 22% to 0 ± 0% while increasing the SpO_2 values. Also, shorter protocols of 5–7 days of 3–8 h of IH indicated to prevent AMS successfully (Kolb et al., 2004; Muza et al., 2006). Nevertheless, it needs to be addressed that these studies were not blinded or placebo-controlled, which may have confounded the outcomes. Those using a placebo-controlled study

design demonstrated to prevent AMS only partially, without significant effects on the primary endpoints of the studies (Schommer et al., 2010; Fulco et al., 2011). While Schommer et al. (2010) found the AMS incidence to be markedly reduced at an altitude of 3611 m, it did not prove to be preventive against AMS when ascending to 4559 m 5 days after a 4-week IH training. Also, Fulco et al. (2011) reported after 7 consecutive nocturnal IH exposures of 7.5 h, at altitudes between 2200 and 3100 m, that the AMS incidence was reduced upon awakening, but the prophylactic effect was not retained for the remaining hours of the day at 4300 m, terrestrial altitude (Fulco et al., 2011). Although they induced ventilatory acclimatization through this protocol, they presumed that the 'sleep' IH protocol might be only effective during sleep and acclimatization in normobaric hypoxia is not effective to prevent AMS in a hypobaric environment (Fulco et al., 2011).

Our findings show at least small preventive effects with regard to the severity of AMS. Ventilatory acclimatization induced by IH might help to prevent AMS development (Beidleman et al., 2004; Burtscher et al., 2008; Muza et al., 2010). Also, our findings point to such a relationship, as the HVR increased after IH in the HG and ΔHVR was associated with the reduction of the LLS. Nevertheless, this relationship was small, indicating that mechanisms other than HVR must be involved in the pathogenesis of AMS. Surprisingly, changes in SpO_2 over the IH sessions were not significant and SpO_2 values were not increased in the HG compared with the PG at POST, although Katayama et al. (2001) reported augmented SpO_2 values up to 7% using the same protocol as we did. Unfortunately, we did not perform blood gas analysis and thus cannot evaluate potential changes in the oxygen dissociation curve (ODC). The outcome of lower mean SpO_2 values in those who developed AMS during the 8-h hypoxic exposure at PRE was also reported by others, demonstrating an inverse relationship between AMS and SpO_2 (Bärtsch et al., 2002; Burtscher et al., 2004; Loeppky et al., 2008; Mairer et al., 2009; Karinen et al., 2010). The relationship between SpO_2 values after 30 min in hypoxia and AMS development at PRE has been reported before by Burtscher et al. (2004), showing SpO_2 values to be approximately 4.9% lower in AMS susceptibles.

Some limitations need to be addressed. Sleep quality was not included into the AMS score, as subjects were only exposed 8 h during the day. The AMS score would probably be one or two points higher in a real altitude setting, including an overnight stay and exercising at altitude (Roach et al., 1996). Due to technical problems, HVR measurements of four subjects, two from the PG and two from the HG, had to be excluded. As mentioned earlier, because no measurements of blood gases are available, potential changes in the ODC cannot be evaluated. Two subjects who were vomiting at PRE, but who did not have headache, were classified as having AMS. Some proposed that headache must be a required symptom for the diagnosis of AMS (Roach et al., 2011), but it needs to be considered that subjects without headache might as well be seriously affected by the altitude (West, 2011). Nevertheless, the relatively large sample size and the exposure to severe normobaric hypoxic conditions strengthen our study findings.

Perspectives

Our results indicate that a short-term IH protocol can at least slightly reduce the severity of AMS during a subsequent 8-h exposure to normobaric hypoxia. This reduction is associated with an increase in hypoxic chemosensitivity, although the relationship is minor. This indicates that mechanisms other than the HVR must be involved in the pathogenesis of AMS. Furthermore, it needs to be assessed if the tested IH protocol can reduce AMS symptoms in a higher risk setting, such as in a hypobaric, hypoxic environment with longer exposure time, including exercise, etc. As the study was performed in normobaric hypoxia, no firm conclusion on whether the tested IH protocol might be effective to reduce AMS when ascending a mountain can be derived. Also, the "optimal dose" of IH for the prevention of AMS and how long effects can be retained need to be determined.

Key words: altitude illness, acclimatization, normobaric hypoxia, hypoxic chemosensitivity.

Acknowledgements

We thank the University of Innsbruck, the Tyrolean Science Fund, the Austrian Society for Alpine and High Altitude Medicine (ÖGAHM), and the Eduard Wallnöfer Foundation for their financial support of the project. We would also like to thank all the volunteers who reserved a great amount of time to participate in the study and those who helped with the IH acclimatization protocol. The authors have no conflict of interest or financial ties to disclose.

References

Bailey DM, Roukens R, Knauth M, Kallenberg K, Christ S, Mohr A, Genius J, Storch-Hagenlocher B, Meisel F, McEneny J, Young IS, Steiner T, Hess K, Bärtsch P. Free radical-mediated damage to barrier function is not associated with altered brain morphology in high-altitude headache. J Cereb Blood Flow Metabol 2006: 26 (1): 99–111.

Bärtsch P, Bailey DM, Berger MM, Knauth M, Baumgartner RW. Acute mountain sickness: controversies and advances. High Alt Med Biol 2004: 5: 110–124.

Bärtsch P, Swenson E, Paul A, Jülg B, Hohenhaus E. Hypoxic ventilatory response, gas exchange, and fluid balance in acute mountain sickness. High Alt Med Biol 2002: 4: 361–376.

Beidleman B, Muza S, Fulco C, Cymerman A, Ditzler D, Stulz D, Staab J, Skrinar G, Lewis S, Sawka M.

Intermittent altitude exposures reduce acute mountain sickness at 4300m. Clin Sci 2004: 106 (3): 321–328.

Benoit H, Germain M, Barthelemy J, Denis C, Castells J, Dormois D, Lacour J, Geyssant A. Pre-acclimatization to high altitude using exercise with normobaric hypoxic gas mixtures. Int J Sports Med 1992: 13 (Suppl. 1): 213–216.

Bernardi L, Passino C, Serebrovskaya Z, Serebrovskaya T, Appenzeller O. Respiratory and cardiovascular adaptations to progressive hypoxia; effect of interval hypoxic training. Eur Heart J 2001: 22: 876–886.

Burtscher M, Brandstätter E, Gatterer H. Preacclimatization in simulated altitudes. Sleep Breath 2008: 12: 109–114.

Burtscher M, Flatz M, Faulhaber M. Prediction of susceptibility to acute mountain sickness by SaO_2 values during short-term exposure to hypoxia. High Alt Med Biol 2004: 5 (3): 335–340.

Casas M, Casas H, Pages T, Rama R, Ricart A, Ventura JL, Ibanez J, Rodriguez FA, Viscor G. Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. Aviat Space Environ Med 2000: 71: 125–130.

Dehnert C, Boehm A, Menold E, Grigoriev I, Bärtsch P. Simulated altitude during the night reduces severity of acute mountain sickness. Med Sci Sports Exerc 2009: 41: 175.

Foster GE, McKenzie DC, Milsom WK, Sheel AW. Effects of two protocols of intermittent hypoxia on human ventilatory, cardiovascular and cerebral responses to hypoxia. J Physiol 2005: 567: 689–699.

Fulco CS, Muza SR, Beidleman BA, Demes R, Staab JE, Jones JE, Cymerman A. Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude. Am J Physiol Regul Integr Comp Physiol 2011: 300: R428–R436.

Garcia N, Hopkins S, Powell F. Effects of intermittent hypoxia on the isocapnic hypoxic ventilatory response and erythropoiesis in humans. Respir Physiol 2000: 123: 39–49.

Hackett PH, Rennie D, Levine BD. The incidence, importance, and prophylaxis of acute mountain sickness. Lancet 1976: 2: 1149–1154.

Hackett PH, Roach RC. High-altitude illness. N Engl J Med 2001: 345: 107–114.

Karinen HM, Peltonen JE, Kähönen M, Tikkanen HO. Prediction of acute mountain sickness by monitoring arterial oxygen saturation during ascent. High Alt Med Biol 2010: 11: 325–332.

Katayama K, Fujita H, Sato K, Ishida K, Iwasaki K, Miyamura M. Effect of a repeated series of intermittent hypoxic exposures on ventilatory response in humans. High Alt Med Biol 2005: 6: 50–59.

Katayama K, Ishida K, Iwasaki K, Miyamura M. Effect of two durations of short-term intermittent hypoxia on ventilatory chemosensitivity in humans. Eur J Appl Physiol 2009: 105: 815–821.

Katayama K, Sato K, Hotta N, Ishida K, Iwasaki K, Miyamura M. Intermittent hypoxia does not increase ventilation at simulated moderate altitude. Int J Sports Med 2007: 28: 480–487.

Katayama K, Sato Y, Morotome Y, Shima N, Ishida K, Mori S, Miyamura M. Intermittent hypoxia increases ventilation and SaO_2 during hypoxic exercise and hypoxic chemosensitivity. J Appl Physiol 2001: 90: 1431–1440.

Kayser B. Acute mountain sickness in Western tourists around the Thorong pass (5400m) in Nepal. J Wilderness Med 1991: 2: 110–117.

Kolb J, Ainslie P, Ide K, Poulin M. Effects of five consecutive nocturnal hypoxic exposures on the cerebrovascular responses to acute hypoxia and hypercapnia in humans. J Appl Physiol 2004: 96 (5): 1745–1754.

Loeppky J, Icenogle M, Charlton G, Conn C, Maes D, Riboni K, Gates L, Melo M, Roach R. Hypoxemia and acute mountain sickness: which comes first? High Alt Med Biol 2008: 9 (4): 271–279.

Lusina S, Kennedy P, Inglis J, McKenzie D, Ayas N, Sheel A. Long-term intermittent hypoxia increases sympathetic activity and chemosensitivity during acute hypoxia in humans. J Physiol 2006: 573: 961–970.

Maggiorini M, Bühler B, Walter M, Oelz O. Prevalence of acute mountain sickness in the Swiss Alps. BMJ 1990: 301: 853–855.

Mairer K, Wille M, Bucher T, Burtscher M. Prevalence of acute mountain sickness in the Eastern Alps. High Alt Med Biol 2009: 10: 239–245.

Mairer K, Wille M, Burtscher M. The prevalence of and risk factors for acute mountain sickness in the Eastern and Western Alps. High Alt Med Biol 2010: 11: 343–348.

Martin D, Windsor J. From mountain to bedside: understanding the clinical relevance of human acclimatization to high-altitude hypoxia. Postgrad Med J 2008: 84: 622–627.

Murdoch DR. Altitude illness among tourists flying to 3740 meters elevation in the Nepal Himalayas. J Travel Med 1995: 2: 255–256.

Muza SR, Beidleman BA, Fulco CS. Altitude preexposure recommendations for inducing acclimatization. High Alt Med Biol 2010: 11: 87–92.

Muza SR, Fulco CS, Beidleman BA, Staab J, Tapia M, Elliott S, Elliott L, Money A, Cymerman A. Normobaric intermittent hypoxic exposures decrease AMS at 4300m altitude. High Alt Med Biol 2006: 4: 338.

Roach RC, Bärtsch P, Oelz O, Hackett PH, Lake Louise AMS Scoring Consensus Committee. The Lake Louise Acute Mountain Sickness scoring system. In: Sutton JR, Houston CS, Coates G, eds. Hypoxia and Molecular Medicine. Queen City Printers, Burlington VT, 1993: 272–274.

Roach RC, Kayser B, Hackett P. Pro: headache should be a required symptom for the diagnosis of acute mountain sickness. High Alt Med Biol 2011: 12: 21–22.

Roach RC, Loeppky JA, Icenogle MV. Acute mountain sickness: increased severity during simulated altitude compared with normobaric hypoxia. J Appl Physiol 1996: 81: 1908–1910.

Schneider M, Bernasch D, Weymann J, Holle R, Bärtsch P. Acute mountain sickness: influence of susceptibility, preexposure and ascent rate. Med Sci Sports Exerc 2002: 34: 1886–1891.

Schommer K, Wiesegart N, Menold E, Haas U, Lahr K, Buhl H, Bärtsch P, Dehnert C. Training in normobaric hypoxia and its effects on acute mountain sickness after rapid ascent to 4559m. High Alt Med Biol 2010: 11: 19–25.

Sheel AW, MacNutt MJ. Control of ventilation in humans following intermittent hypoxia. Appl Physiol Nutr Metab 2008: 33: 573–581.

Weil JV, Byrne-Quinn E, Sodal IE, Friesen WO, Underhill B, Filley GF, Grover RF. Hypoxic ventilatory drive in normal man. J Clin Invest 1970: 49: 1061–1072.

West JB. Con: headache should not be a required symptom for the diagnosis of acute mountain sickness. High Alt Med Biol 2011: 12: 23–25.